

### **REMARKS**

Claims 1-3, 5, 7-23 and 25-33 were pending in the application. Claims 2, 16, 23 and 32 are canceled herein and new claims 34-36 are added. Upon entry of this amendment, **claims 1, 3, 5, 7-15, 17-22 and 25-36 will be pending.**

Claim 19 is amended to incorporate limitations of claim 23. Claims 25-29 are amended to clarify that the claimed compositions comprise a fragment, *or a variant of a fragment*, of thymosin  $\beta_4$ , wherein the fragment, *or variant of the fragment*, comprises up to 5 conservative amino acid substitutions *in comparison to SEQ ID NO: 1*. Support for these amendments can be found, for example, in original claim 23 and on page 6, lines 31-34; page 16, line 32 to page 17, line 12; and page 21, lines 3-28 of the specification. Claim 25 is further amended to depend from claim 19. Withdrawn claims 3 and 11 are amended to depend from claim 1. Withdrawn claims 5 and 7-9 are amended to properly depend from a single claim. Support for new claims 34-36 can be found in the specification and claims as originally filed (for example, original claims 20-22 and page 11, line 33 to page 12, line 8; page 12, lines 14-19; and page 29, lines 5-19 of the specification).

No new matter has been introduced by these amendments and no amendments are made to distinguish prior art.

### **INFORMATION DISCLOSURE STATEMENT**

The Information Disclosure Statement (IDS) filed July 21, 2004 in connection with this application does not appear to have been considered by the Examiner. Provided with this Amendment and Response is a copy of the Form 1449 submitted with the IDS of July 21, 2004. Applicants request that the references be made of record in the application and that the signed Form 1449 be returned with the next Office action.

### **RESTRICTION REQUIREMENT**

The requirement for restriction between the claims of Group I and Group II has been made final. Applicants note that the restricted claims are related as product (Group II) and process (Group I). As such, upon allowance of an elected product claim(s), Applicants are entitled to rejoinder and examination of all process claims that depend from or otherwise include all limitations of the allowable product claim(s).

## **REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH**

**Claims 19-23 and 25-33** are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. The Office states the claims are drawn to a genus that comprises fragments of thymosin  $\beta_4$ , wherein the fragments comprise amino acid residues 17-23 or 17-22 of SEQ ID NO: 1, and 0 to 5 conservative amino acid substitutions. It is alleged by the Office that the claims encompass numerous species having substantial variability. The Office concludes one of skill in the art would not recognize from the disclosure that Applicants were in possession of the claimed genus of polypeptides. The Office further argues that one cannot readily determine the structural modifications necessary to render a thymosin  $\beta_4$  polypeptide variant a conservative variant.

Claims 23 and 32 are canceled herein, rendering the rejection moot as it pertains to these claims. Applicants traverse this rejection in regard to claims 19-22, 25-31 and 33.

### **Claims 30, 31 and 33**

Claims 30 and 31 are directed to compositions comprising thymosin  $\beta_4$  fragments consisting of amino acid residues 17-23, or 17-22, respectively, of SEQ ID NO: 1. Claim 33 is directed to compositions for promoting hair growth, wherein the compositions comprise a polypeptide consisting of amino acids 1-26; 13-23; 7-43; 13-43; 10-28; 20-43; or 19-26 of SEQ ID NO: 1. These claims do not encompass polypeptides comprising amino acid substitutions, and the polypeptides do not necessarily comprise amino acid residues 17-22 or 17-23. Rather, each of these claims include polypeptides consisting of particular amino acid residues. Furthermore, each of the specific polypeptides is taught in the specification (see, for example, page 30, lines 2-13; page 32, line 20 to page 33, line 5; and Table 2 on page 33 of the specification). Therefore, Applicants submit claims 30, 31 and 33 comply with the written description requirement.

### **Claims 19-22 and 25-29**

Claim 19 is directed to a composition for promoting hair growth in a subject, wherein the composition comprises a polypeptide of no more than 10 amino acid residues in length comprising an actin-binding peptide, wherein the polypeptide comprises a fragment of thymosin  $\beta_4$ , or a variant of the fragment that enhances hair growth in the subject. Dependent claims 20-22

are directed to pharmaceutical compositions comprising the thymosin  $\beta_4$  polypeptides. Claims 25-29 specify that the thymosin  $\beta_4$  fragment, or variant of the fragment, comprises amino acid residues 17-23 or 17-22 of SEQ ID NO: 1, and comprises 0 to 5, 0 to 4, 0 to 3 or 0 to 2 conservative amino acid substitutions in comparison to SEQ ID NO: 1.

The specification provides more than adequate written descriptive support for the pending claims, including thymosin  $\beta_4$  fragments and variants of fragments comprising conservative amino acid substitutions. For example, the paragraph on page 21, lines 3-28, teaches that homologs and fragments of thymosin  $\beta_4$  (SEQ ID NO: 1) are useful for promoting hair growth, and these fragments and variants can comprise amino acid substitutions within and/or outside of the actin-binding domain. The cited paragraph further provides examples of conservative amino acid substitutions that preserve activity of the peptides and lists a number of specific examples of peptides falling within the scope of the claims. The paragraph continues by stating that comparison of thymosin  $\beta_4$  sequences “provides guidance about amino acid substitutions that can be made in the T $\beta_4$  acting-binding domain while preserving its therapeutic activity.” This passage further provides specific examples of residues that are not good candidates for substitution (*i.e.* residues at positions 1, 3 and 4) due to their high level of conservation. Furthermore, the specification provides a table of specific examples of conservative amino acid substitutions that can be introduced into the thymosin  $\beta_4$  polypeptides (see page 13 of the specification).

In addition, the specification provides specific examples of thymosin  $\beta_4$  fragments and variants. For example, the specification teaches thymosin  $\beta_4$  polypeptides of 10 amino acids or less in length, including T $\beta_4$ <sup>19-26</sup>, T $\beta_4$ <sup>17-23</sup> and T $\beta_4$ <sup>17-22</sup> (see page 30, lines 2-13; page 32, line 20 to page 33, line 5; and Table 2 on page 33 of the specification). The specification further teaches specific variants of thymosin  $\beta_4$ , such as  $\beta_4^{\text{Ala}}$ , which comprises a serine to alanine substitution (which is a conservative amino acid substitution) at position 1, and other  $\beta$ -thymosin family members, including  $\beta_9$  and  $\beta_{10}$ , which comprise the actin-binding site LKKTET, but have amino acid changes at other residues. Each of these variant thymosin polypeptides were shown to promote hair growth (see Table 1 on page 33). Therefore, given the teachings of the specification, it would have been clear to one of skill in the art that Applicants were in possession of the full scope of the claims at the time the application was filed.

## **Variants**

The Office further states that the metes and bounds of the fragments or variants is unclear and one cannot readily determine the structural modifications necessary to render a polypeptide variant a conservative variant. Applicants respectfully point out that the pending claims recite “variant” thymosin  $\beta_4$  polypeptides, not “conservative variant.” The specification teaches that “variant” thymosin  $\beta_4$  polypeptides include polypeptides having conservative and non-conservative amino acid substitutions (see the definition on page 16, line 32 to page 17, line 9). Furthermore, the specification provides specific examples of conservative amino acid changes (see, for example, page 13, lines 13-35), and these types of changes are well known in the art. Therefore, Applicants submit the metes and bounds of the claimed thymosin  $\beta_4$  polypeptide fragments and variants is clear.

## **Summary**

Given the thorough description in the specification of thymosin  $\beta_4$  fragments, and variants of fragments, as well as specific examples of the claimed polypeptides, one of skill in the art would recognize Applicants to be in possession of the full breadth of the pending claims. Accordingly, Applicants request withdrawal of this rejection under 35 U.S.C. §112, first paragraph.

## **REJECTION UNDER 35 U.S.C. §112, SECOND PARAGRAPH**

**Claims 25-29 and 32** are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. The Office alleges it is unclear how the claimed peptides can comprise residues of SEQ ID NO: 1 and have substitutions.

Claim 32 is cancelled herein, rendering the rejection moot as it pertains to this claim. Claims 25-29, and withdrawn claims 5 and 7-9, are amended herein to clarify that the claimed compositions comprise polypeptides which are fragments of thymosin  $\beta_4$ , *or variants of fragments of thymosin  $\beta_4$  comprising the recited amino acid residues.* The claims further specify that the fragment or variant of the fragment can include up to 5 conservative amino acid substitutions *in comparison to* SEQ ID NO: 1. The specification teaches that variants of thymosin  $\beta_4$  can comprise amino acid substitutions in comparison to SEQ ID NO: 1 (see, for example, page 16, line 33 to page 17, line 1 of the specification) and that the disclosed

polypeptides can comprise conservative amino acid substitutions within the actin-binding domain and/or outside of the actin-binding domain (see, for example, page 10, lines 22-27, and page 21, lines 3-18). Therefore, Applicants submit it is clear that the pending claims encompass thymosin  $\beta_4$  fragments, and variants of fragments, comprising amino acid substitutions relative to SEQ ID NO: 1. Accordingly, Applicants request withdrawal of this rejection under 35 U.S.C. §112, second paragraph.

## REJECTION UNDER 35 U.S.C. §102

**Claims 19-23 and 25-32** are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Kleinman *et al.* (WO 00/06190). The Office alleges Kleinman *et al.* disclose a composition comprising a polypeptide comprising the amino acid sequence LKKTET and conservative variants thereof, and further disclose administering the polypeptide in a topical formulation comprising a hydrogel. Claims 23 and 32 are canceled herein, rendering the rejection moot as it pertains to these claims. Applicants traverse this rejection in regard to claims 19-22 and 25-31.

In order to anticipate a claim, a cited reference must teach each and every limitation of the claim. As recited herein, claim 19 is directed to a composition for promoting hair growth in a subject, wherein the composition comprises a polypeptide of **no more than 10 amino acid residues in length** comprising an actin-binding peptide, wherein the polypeptide comprises a **fragment** of thymosin  $\beta_4$ , or a variant of the fragment that enhances hair growth in the subject. The remainder of the rejected claims depend directly or indirectly from claim 19.

Although Kleinman *et al.* describe a polypeptide that comprises the sequence LKKTET, and conservative variants thereof, the reference teaches only the full-length thymosin  $\beta_4$  polypeptide comprising the recited amino acid sequence. Kleinman *et al.* do not teach or even suggest polypeptides of *no more than 10 amino acids in length* or fragments of thymosin  $\beta_4$  polypeptides. In addition, Kleinman *et al.* do not teach any compositions for promoting hair growth in a subject. In contrast to Kleinman *et al.*, the instant application describes specific thymosin  $\beta_4$  polypeptides of 10 amino acids or less in length (such as T $\beta_4$ <sup>19-26</sup>, T $\beta_4$ <sup>17-23</sup> and T $\beta_4$ <sup>17-22</sup>), and teaches that such fragments are effective for promoting hair growth (see, for example, page 30, lines 2-13; page 32, line 20 to page 33, line 5; and Table 2 on page 33 of the specification).

Since Kleinman *et al.* do not teach every element of the rejected claims, the claims are not anticipated. Accordingly, Applicants request withdrawal of this rejection under 35 U.S.C. §102(b).

## **DOUBLE PATENTING**

**Claims 19-23 and 25-33** are rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 3-5 and 29 of U.S. Pre-Grant Publication No. 2004/0220111. The Office alleges that although the claims are not identical, they are not patentably distinct. Applicants traverse this rejection.

U.S. Pre-Grant Publication No. 2004/0220111 is a continuation of, and therefore contains the same disclosure as, Kleinman *et al.*, which was cited by the Office in connection with the rejection under 35 U.S.C. §102(b). As discussed above, Kleinman *et al.* do not teach or even suggest polypeptides of no more than 10 amino acids in length, nor any fragments of the thymosin  $\beta_4$  polypeptide. Kleinman *et al.* also do not teach any compositions for promoting hair growth in a subject. Furthermore, Kleinman *et al.* do not teach any of the specific polypeptides recited in claim 33. Therefore, Applicants submit the pending claims are patentably distinct from the claims of U.S. Pre-Grant Publication No. 2004/0220111 and request withdrawal of the double patenting rejection.

## CONCLUSION

It is respectfully submitted that the present claims are in a condition for allowance. Should the Examiner have further questions or comments with respect to examination of this case, it is requested that the Examiner telephone the undersigned so that further examination of this application can be expedited.

Respectfully submitted,

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